

Acute Dialysis Quality Initiative

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Workgroup 4

Minimizing Impact of Renal Replacement Therapy on Recovery of Acute Renal Failure

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Introduction

Although renal replacement therapy (RRT) is the mainstay of supportive care in patients with severe acute renal failure (ARF), performance of this life-sustaining treatment can have untoward effects that contribute to the prolongation of renal failure or impede the ultimate recovery of renal function. Renal biopsies in patients with prolonged ARF managed using hemodialysis demonstrated regions of fresh tubular necrosis days to weeks after the initial inciting insult [1,2]. Both dialysis-associated hypotension and the activation of cellular and humoral mediators by exposure to the extracorporeal circuit have been proposed mechanisms of this ongoing parenchymal injury [2.]. Access catheter-associated complications, metabolic, and electrolyte disturbances related to the performance of RRT may also impact on outcomes in patients with ARF.

In evaluating strategies to minimize the impact of RRT on the recovery of renal function in ARF, the workgroup created an inventory of complications associated with RRT. This process identified potential mechanisms by which RRT itself might contribute to the prolongation of renal injury, and correlated these mechanisms with the identified or published complications of therapy. The workgroup then evaluated how the processes of RRT can be modified to decrease the risk of further injury to the kidney, addressing both selection of therapy modality and factors within the function of each that may contribute to ongoing renal injury. While this review was based on existing literature, the workgroup noted that there is a paucity of high-level data (e.g., large randomized controlled trials) on which to base any conclusions. The workgroup therefore identified many areas for future research.

What are the common adverse effects associated with RRT's?

The workgroup identified a wide range of complications associated with the use of RRT (Table 1). These complications could be divided into broad categories including those related to vascular or peritoneal access, complications related to the extracorporeal circuit, hemodynamic compromise, electrolyte and metabolic complications and complications related to human error.

What mechanisms prolong the course of renal injury during renal replacement therapy?

The mechanisms that prolong the course of renal injury during RRT are incompletely understood. Potential mechanisms are summarized in Table 2. Decreased renal perfusion as a result of hemodynamic changes during RRT has been most commonly implicated as a mechanism for prolongation of renal injury [2,3]. Autoregulation of renal blood flow is impaired in animal models of ischemia-reperfusion injury. The normal response to decreased renal perfusion pressure is vascular dilatation, decreasing renal vascular resistance and allowing maintenance of renal blood flow. Following renal ischemia-reperfusion injury, this vasodilatory response is attenuated or replaced by frank vasoconstriction, resulting in a marked decrement in renal blood flow in response to small changes in perfusion pressure [4,5]. Hypotension is a common complication of RRT, particularly in critically ill patients with underlying hemodynamic compromise, mediated by intravascular volume depletion; intercompartmental fluid shifts and decreased cardiac output. Alterations in regional blood flow may also lead to decreased renal perfusion despite maintenance of systemic arterial blood pressure.

The activation of cellular and humoral pathways of inflammation has also been implicated in the prolongation of renal injury. The role of biocompatibility of the extracorporeal circuit has been suggested in both animal [6,7] and human studies [8-10], although the results of clinical trials have been variable [11,12]. Other mediators of inflammation during RRT may include exposure to non-membrane components of the extracorporeal circuit (pump and tubing segment, air interface), microbiological contamination of the extracorporeal circuit, access-associated infections and allergic reactions.

Exposures to endogenous or exogenous toxins during RRT are uncommon, but may also contribute to renal injury. Pigment nephropathy may be caused by either rhabdomyolysis or hemolysis. Access-related vascular thrombosis, and severe hypokalemia or hypophosphatemia may precipitate rhabdomyolysis. Hemolysis may be caused by mechanical trauma in the extracorporeal circuit such as by kinking of tubing, or roller pump and shear stress on blood [13-15]. Hemolysis may also be caused by, treatment-related electrolyte disturbances, thermal injury during treatment or chemical contamination of dialysate or replacement fluids.

Which of these adverse effects have the greatest impact on prolongation or prevention of renal recovery?

Rigorous data allowing precise categorization for impact of adverse effects during RRT on the prolongation of renal injury or prevention of renal recovery are not available. Recognizing this limitation, the workgroup categorized adverse events as occurring with high, low or unknown frequency and the impact of these adverse events as high, low or unknown impact. (Table 3).

The workgroup identified RRT related hemodynamic compromise and catheter associated infections as high frequency, high impact complications. The inclusion of catheter-associated infection in this category is with the caveat that although catheter-associated infection is thought to be strongly associated with morbidity and mortality in critically ill patients, specific data regarding the impact of catheter-associated infections on renal recovery do not exist [16-18]. Access malfunction and anticoagulation-associated complications also occur with high frequency, but were judged to have a relatively low-impact on recovery of renal function, however additional data are required to better define this impact.

Although early studies suggested that membrane bioincompatibility has a major impact on both survival and recovery of renal function in patients with ARF treated with intermittent hemodialysis [8-10]. Meta analyses of multiple studies have not confirmed these findings, with one analysis finding a survival benefit of synthetic membranes as compared to cuprophane [11] while another found no difference [12]. Neither study identified an impact on recovery of renal function [19].

Catheter-associated hemorrhage, vascular injury and visceral organ injury are associated with significant morbidity and have the potential for high impact on delayed or reduced renal recovery. However these complications occur with very low frequency. Similarly, membrane-associated bradykinin activation, resulting in anaphylactoid reactions can result in hypotension and recurrent renal ischemia, but occur very uncommonly [20,21]. Muscle injury from catheter-associated thrombosis and hemolysis from mechanical dysfunction or chemical contamination occur with very low frequency and do not have a substantial impact of recurrent renal injury. It should be noted, however, that the frequency of chemical contamination of water for acute hemodialysis is unknown. Water quality for hemodialysis in critical care units may not be reported, and is complicated by the common use of portable reverse osmosis water treatment units, which may not provide the same level of water quality as achieved using permanent water treatment systems. Overt microbiological contamination of the extracorporeal circuit occurs with low frequency, however the frequency of low-level endotoxin contamination of dialysate is unknown. The impact of this contamination on recovery of renal function has not been studied and may be difficult to quantify in the critically ill with many invasive vascular lines and low-grade sepsis a common occurrence [18]. Acid-base disturbances as a result of RRT are uncommon, and have an unknown impact on renal recovery.

The frequency of many potential complications of RRT in ARF is unknown due to the absence of reporting systems. As the result, the frequency of human error in the RRT process and its impact on renal recovery is not known. However, anonymous incident reporting used in some ICUs can provide insight into the human errors related ICU care [22,23], and to the extent reported the performance of CRRT [24]. These data suggest that human errors may have significant impact on outcomes. Similarly, the precise frequency of electrolyte complications is unknown, however they are unlikely to play a major role in prolonging renal injury. Due caution should be taken to prevent these predictable complications. There are also insufficient data to evaluate either the frequency or impact for a large number of potential complications despite anecdotal reports and experience by clinicians. This includes vitamin and micronutrient depletion, amino acid depletion, hormone depletion, altered glycemic control and abnormal thermal balance.

Are there patient specific risk factors that impact these adverse effects?

Data regarding patient specific risk factors that impact on these adverse events are not available. While patients with cardiac dysfunction or peripheral vascular disease are at increased risk of hemodynamic instability during RRT, there are no data to substantiate an increased risk of non-recovery of renal function related to these patient factors and complications of RRT. Similarly, although superimposition of acute injury on chronic kidney disease is associated with decreased recovery of renal function [25], the impact of RRT on this outcome is unknown.

Is there a relationship between modality of therapy and risk for ongoing injury to the kidney?

Recovery of renal function has been evaluated as a secondary outcome in several trials comparing intermittent hemodialysis (IHD) to continuous renal replacement therapy (CRRT). CRRT is thought to afford greater hemodynamic stability than intermittent hemodialysis, particularly in critically ill patients with underlying hemodynamic compromise [26]. This was recently demonstrated in a prospective randomized trial of 80 patients in which CVVHD was associated with a small increase in mean arterial blood pressure (MAP) as compared to a fall in MAP during IHD despite greater net fluid removal during CRRT [27]. Despite the greater hemodynamic stability in the CRRT treated patients, this study did not detect any difference in survival or recovery of renal function between groups.

However, several other studies have suggested improved recovery of renal function in surviving patients, despite being unable to demonstrate a survival benefit associated with CRRT. In a prospective randomized trial of 166 patients, Mehta *et al* reported survival of 50.7% of patients who received an “adequate” exposure to therapy (defined as at least 2 3-hour IHD sessions or 25 hours of CRRT) in the IHD group and 34.4% in the CRRT group [28]. Complete recovery of renal function was observed in 29.9% of patients receiving “adequate” therapy in the IHD group and 25% in the CRRT group. Adjusting for the differences in survival between the two groups, 59% of surviving IHD patients had complete recovery of renal function as compared to 73% of patients in the CRRT group ($p>0.05$).

In a retrospective analysis of 261 patients in two tertiary intensive care units Manns *et al.* observed a mortality of 71.9% in 178 patients treated with CRRT and compared to 42.2% in 83 patients treated with IHD [29]. In hospital recovery of renal function was observed in 28.6% of the CRRT patients as compared to 39.8% of the IHD patients ($p=0.07$). When analyzed in terms of patients alive at the time of hospital discharge, recovery of renal function was observed in 80% of the patients treated with CRRT as compared to 62.5% of patients treated with IHD ($p=0.06$).

A recent retrospective study from Alberta, Canada also found that recovery of renal function was more frequent in surviving patients who were treated with CRRT as compared to IHD [30]. Of 28 patient treated with IHD, hospital survival was 50% as compared to 37% of the 65 patients treated with CVVH. Only 5 of the 14 (36%) surviving patients treated with IHD recovered renal function as compared to 21 of the 24 (87%) surviving patients treated with CRRT. As with the previously described studies, limiting analysis of recovery of renal function to surviving patients does not take into account the competing risk of mortality. When analyzed in terms of the combined outcome of death or non-recovery of renal function, the difference between groups was not statistically significant.

Poling the data from these three studies demonstrates recovery of renal function in 80.2% of surviving patients treated with CRRT as compared to 57.9% of patients treated with IHD ($p<0.001$). However, when analyzed based on the combined outcome of death or non-recovery of renal function no benefit is observed, with 25.1% of CRRT patients discharged from the hospital with recovered renal function as compared to 30.9% of patients treated with IHD ($p=0.17$). Thus, although the recovery of renal function is higher in surviving patients treated with CRRT, no overall benefit can be ascribed to either modality when the competing mortality risk is taken into account. There are no data comparing recovery of renal function in ARF patients treated with peritoneal dialysis (PD) or sustained low-efficiency daily dialysis (SLEDD) to outcomes with other modalities of therapy. The workgroup therefore made no recommendations regarding selection of modality of therapy to reduce the risk of ongoing renal injury. Further data from large, prospective, randomized trials are needed to answer this question

Does the dose of renal replacement therapy impact on the recovery of renal function?

In a randomized controlled trial of 425 patients with ARF treated with three dose strata of continuous venovenous hemofiltration (CVVH) as assessed by ultrafiltration rate (doses: 20 mL/kg/hr, 35 mL/kg/hr, and 45 mL/kg/hr), recovery of renal function in surviving patients was 95%, 92% and 90% ($p=NS$) [31]. In a comparison of daily to every-other-day IHD, recovery of renal function was observed in all patients, however the time to recovery of renal function was shorter in the daily (9 ± 2 days), as compared to the every-other-day treatment group (16 ± 6 days, $p=0.001$) [32]. The mean ultrafiltration volume was 1.2 ± 0.5 L in the daily dialysis group as compared to 3.5 ± 0.3 L in the every-other-day treatment group ($p<0.001$). Hypotension occurred in 5 ± 2 percent of treatment sessions in the daily treatment arm as compared to 25 ± 5 percent of treatment sessions in the every-other-day treatment group ($p<0.001$). Thus, daily hemodialysis may mitigate ongoing renal injury by decreasing per-treatment ultrafiltration requirements and decreasing the frequency of intradialytic hypotension. These results need to be confirmed in additional clinical trials.

Can the use of specific techniques within each modality prevent additional renal injury?

Multiple strategies to minimize complications of therapy might have benefit in preventing additional renal injury during renal replacement therapy. These strategies include those to prevent catheter-associated infections such as local catheter care and dressing techniques, the use of antibiotic locking solutions or antimicrobial-impregnated catheters, and avoidance of the femoral catheter site [33,34]. None of these strategies have been specifically evaluated with regard to their impact on recovery of renal function. Similarly, strategies to minimize the occurrence of hypotension during therapy, monitoring of hemodynamic parameters, sodium modeling during therapy, cooling of dialysate, minimizing the rate of ultrafiltration and the use of bicarbonate buffered dialysate and replacement fluids for all modalities of RRT, may have benefit with regard to renal recovery [3]. This relationship between RRT mediated hypotension and reduced renal recovery has not been adequately evaluated in clinical trials, and may never be due to the study design and sample size required

Although the role of human error as a cause of adverse outcomes during RRT and prolongation of renal injury is poorly documented, the principle of *primum non nocere* mandates the minimization of errors. It is important to recognize that the root cause of most errors is related to system design factors. While clearly established policies and protocols and an educational process for nurses performing RRT [35] are necessary, ongoing assessment of the

care process, including design of the human-machine interface, is necessary to minimize the risk of human error [36].

Are there specific management considerations in the pediatric patient?

Although data from randomized trials in pediatric patients do not exist to evaluate and recommend specific RRT treatment practices for minimization of the risk of ongoing renal injury, recent data are available to lend insight into best practices for the management of RRT in pediatric patients.

Circuit Priming for the Small Pediatric Patient

Circuit priming with whole blood is recommended to minimize cardiovascular instability at CRRT initiation for smaller pediatric patients (usually less than 10-15 kg) for whom the CRRT extracorporeal circuit volume is greater than 10% of the patient total blood volume. Blood priming for AN69 membranes may potentiate the bradykinin release syndrome as a result of the low pH and citrate concentration of banked blood. Recent protocols using bicarbonate buffering and calcium replacement or circuit prime buffering have been devised to minimize this phenomenon. [37,38].

Anticoagulation

Heparin and citrate CRRT circuit anticoagulation predominate in North American pediatric CRRT programs. While both methods offer similar CRRT circuit survival times, recent data from a multi-center collaborative effort demonstrate that citrate anticoagulation was associated with few patient side effects whereas a significant number of patients receiving CRRT circuits with heparin anticoagulation had CRRT discontinued in the presence of systemic bleeding [39].

Solution Errors

As noted previously, accurate assessment of human error rates is nearly impossible in CRRT since it is difficult to quantify the denominator. However, a recent survey of pediatric CRRT programs on three relevant listserves revealed that errors in CRRT dialysis fluid or replacement fluid composition do exist and in some cases have been thought to be associated with poor outcomes [40]. This potential complication is clearly not limited to pediatric patients. Prevention of such errors is now simple since numerous industry made bicarbonate based solutions are available.

Non-Renal Indications for CRRT in the Pediatric Patient

CRRT is being more commonly in children used for non-renal indications such as drug intoxication [41] and hyperosmolar conditions [42]. In addition, both intermittent hemodialysis and CRRT are commonly used for treatment of hyperammonemia associated with inborn errors of metabolism [43]. Careful attention to serum electrolyte concentrations, especially potassium and phosphorus is critical when providing renal replacement therapy to patients without acute renal failure since both HD and CRRT will result in electrolyte depletion in this population. Electrolyte supplementation, either intravenously or in the dialysis/ replacement solution is often required to maintain normal serum levels.

Conclusions

Consensus Statements

The impact of RRT on the course of ARF is incompletely understood. Although a large number of potential mechanisms for renal injury during RRT can be implicated, precise assessment of their impact on prolongation of renal injury or prevention of renal recovery is not possible.

Hemodynamic instability during RRT and access-related complication, particularly access-related bacteremia, are likely to have the highest impact (Grade E). Although membrane biocompatibility has also been suggested as playing a major role in outcomes of ARF, analysis of the data does not demonstrate a clear impact on recovery of renal function (Grade C).

The modality of RRT has also been suggested as having an impact on renal recovery, with suggestion that CRRT is associated with greater recovery of renal function in survivors than IHD. When analyzed on the basis of the combined outcome of mortality or non-recovery of renal function, the data does not favor either modality (Grade A).

Similarly, although studies have suggested improved survival with higher doses of CRRT and IHD, a definitive impact of dose of therapy on recovery of renal function has not been demonstrated (Grade B).

Recommendations for Clinical Practice

Clinical recommendations must therefore be limited to the broad admonishment that complications during RRT, including hemodynamic instability and catheter-related bacteremia, be minimized by using best clinical practices, while recognizing that the impact of specific practices on recovery of renal function have not been evaluated. The data do not support recommendations regarding modality of renal replacement therapy (Grade A), utilization of specific membrane (Grade C) or dose of therapy (Grade B).

Recommendations for Future Research

Future clinical trials of RRT in ARF must specifically consider the impact of interventions on recovery of renal function, adjusting for the competing risk of mortality. Specific issues that need to be studied include the efficacy of strategies to enhance hemodynamic stability during RRT, the efficacy of strategies to reduce access related complications and the impact of dose and modality of therapy on recovery of renal function in ARF.

Table 1: Complications of Renal Replacement Therapy

Access Related Complications

Infection

- Local (exit site, subcutaneous tunnel)
- Systemic (bacteremia, sepsis)
- Peritonitis (in peritoneal dialysis)

Hemorrhage

- Catheter-associated vascular thrombosis
- Vascular or visceral organ injury
- Access malfunction

Extracorporeal Circuit Associated Complications

Bio-incompatibility

- Membranes
- Non-membrane surfaces
- Endotoxin contamination

Mechanical dysfunction

- Hemolysis
- Air embolization
- Extracorporeal blood loss
- Fluid-balance errors

Microbiological contamination

Chemical contamination

- Dialysate and Replacement Fluids
- Sterilant

Anticoagulation

- Inadequate anticoagulation/thrombosis
- Excessive anticoagulation/hemorrhage
- Complications of specific agents
 - Heparin-associated thrombocytopenia
 - Citrate-associated metabolic alkalosis and hypocalcemia

Hemodynamic Compromise/Hypotension

- Volume depletion
- Solute dysequilibrium
- Vasodilation
- Increased intra-abdominal pressure (peritoneal dialysis)

Electrolyte and Metabolic Complications

Prescriptive errors

- Errors in compounding fluids
- Electrolyte depletion states associated with RRT
 - Hypophosphatemia
 - Hypokalemia
 - Hypomagnesemia

Acid-base disturbances

- Selection and concentration of buffer
- Citrate anticoagulation
- High-volume replacement fluids

Vitamin and micronutrient depletion

- Water soluble vitamins
- Trace minerals
- Carnitine

Hormone depletion

- Glucocorticoids

Glycemic control

- Hyperglycemia
- Hypoglycemia

Amino acid depletion

Thermal balance

- Hypothermia
- Masking of hyperpyrexia

Human Factors

- Physician error
 - Nursing error
 - Pharmacist error
 - Biomedical technician error
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Table 2: Mechanisms of Renal Injury during RRT

Mechanism of Renal Injury	Contributory Processes During RRT
	<i>Hemodynamic Factors</i>
Intravascular volume depletion	Intravascular volume depletion from ultrafiltration
Decreased cardiac output	Fluid compartment shifts due to solute dysequilibrium
Altered regional blood flow	Increased intra-abdominal pressure (peritoneal dialysis)
Systemic hypotension	Access related complications <ul style="list-style-type: none"> Infection Hemorrhage Vascular/visceral organ injury <ul style="list-style-type: none"> -hemorrhage -pneumothorax -pericardial tamponade
	Extracorporeal-circuit associated complications <ul style="list-style-type: none"> Bioincompatibility <ul style="list-style-type: none"> -bradykinin release -allergic reactions Mechanical dysfunction <ul style="list-style-type: none"> -disconnection -air embolization -pump and balance errors Microbiological contamination <ul style="list-style-type: none"> -endotoxin exposure Chemical Contamination <ul style="list-style-type: none"> -sterilant exposure -allergic reaction to preservatives Anticoagulation <ul style="list-style-type: none"> -reactions to nafamostat and prostenoids
	Electrolyte complications <ul style="list-style-type: none"> Hypokalemia Hyperkalemia Hypomagnesemia Hypophosphatemia
	Metabolic complications <ul style="list-style-type: none"> Use of acetate-buffered fluids Glucocorticoid deficiency Thermal-mediated central vasodilatation
	Human factors

Table 2: Mechanisms of Renal Injury during RRT

Mechanism of Renal Injury	Contributory Processes During RRT
	<i>Activation of Inflammatory Pathways</i>
Activation of cellular mediators	Extracorporeal-circuit associated complications
Activation of humoral mediators	Bioincompatibility
Cytokines	-membrane
Kinin-kininogen system	-non-membrane surfaces
Coagulation cascade	-endotoxin contamination
Complement system	Microbiological contamination
	Allergic reactions
	-membrane/circuit
	-ethylene oxide
	-anticoagulants
	Access related complications
	Infection
	-local
	-systemic
	Vascular/visceral organ injury
	-bowel perforation (peritoneal dialysis)
	Human factors
	<i>Exposure to Toxins</i>
Endogenous toxins	Extracorporeal-circuit associated complications
Hemoglobin	Mechanical dysfunction with hemolysis
Myoglobin	Chemical contamination
Exogenous toxins	-chloramines (hemolysis)
	-nitrates/nitrites (methemoglobinemia)
	-copper (hemolysis)
	Access related complications
	Vascular thrombosis
	-arterial thrombosis with rhabdomyolysis
	-venous thrombosis with compartment syndrome
	Access malfunction
	-elevated access pressures leading to hemolysis
	Electrolyte complications leading to hemolysis or rhabdomyolysis
	Severe hypokalemia
	Severe hypophosphatemia
	Hemolysis due to hyperthermia
	Human factors

Table 3: Impact of RRT Complications on Prolongation of Renal Injury

	High Impact	Uncertain Impact	Low Impact
High Frequency	Hemodynamic compromise Catheter associated infection		Access malfunction Anticoagulation-associated complications Membrane bioincompatibility
Unknown Frequency	Human error	Vitamin and micronutrient depletion Hormone depletion Amino-acid depletion Hyperglycemia Impaired thermal balance Peritonitis (peritoneal dialysis)	Electrolyte complications
Low Frequency	Catheter-associated hemorrhage Catheter-associated vascular/visceral organ injury Membrane-associated bradykinin activation	Microbiological contamination* Acid-base disturbances	Catheter-associated thrombosis Mechanical dysfunction Chemical contamination

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